UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,721	09/05/2003	Xiaowu Pang	NIH202.001C1	8676

20995 7590 10/11/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SALVOZA, M FRANCO G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,721	PANG ET AL.	
	Examiner	Art Unit	
	M. Franco Salvoza	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1,3-7,9-15 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 8, 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, species dengue 2, DeltaME deletion) in the reply filed on July 17, 2006 is acknowledged. The traversal is on the ground(s) that the members of the group are sufficiently few in number that a search and examination can be made without creating a serious burden. This is not found persuasive because as clarified in the Restriction Action, the other Group and species recite independent and structurally distinct inventions and separate searches would be required for each, constituting an undue search burden. The Restriction is necessary for a proper and thorough examination of the claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 3-7, 9-15, 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 17, 2006.

Claims 2, 8, 16-20 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites "substantially all of the nonstructural region." It is unclear what applicant intends by "substantially all."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the whole 5'UTR; the whole NS region; the whole 3'UTR; and all of the structural proteins to encapsulate the subgenomic replicon, does not reasonably provide enablement for fragments or part of the 5'UTR, substantially all of the NS region, part of the 3'UTR, or which structural proteins are sufficient to encapsulate said replicon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 P 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988) and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed

most relevant should be considered.

In this case, the amount of direction or guidance presented, the absence of working examples, the state of the prior art and the breadth of the claims are most relevant.

As indicated above, claim 16 broadly recites part of all of the 5'UTR and 3'UTR; substantially all of the nonstructural region. Additionally, a recitation to structural proteins wherein said proteins encapsulate said subgenomic replicon, read on any combination of minimal structural proteins.

References reviewing the state of the art for these particular diseases indicate that deletions in these portions still have varying results in terms of virulence and replication. For example, Proutski et al. indicates that after deletion analysis almost the entire 3'UTR is essential for optimal functioning rather than the most 3' terminal sequences (p. 122). Further, the terminal portions tend to have more promoter-like functions while other sequences have more enhancer functions. Additionally, Khromykh et al. (2000) teaches deletion constructs for the NS proteins, when complemented, had varying efficiencies (p. 3253). Corver et al. indicates that certain 5' regions are required for replication for Yellow Fever that differ from the core sequences conserved among all flaviviruses.

Applicant's disclosure does not contain minimal examples of domains, positions, fragments of said domains (the UTRs or NS regions) that are sufficient for replication and/or to maintain sufficient virulence, or which of any structural proteins minimally will be sufficient to encapsulate said replicon.

In view of these factors, the application has not provided sufficient information to enable those in the art to practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 8, 17-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Westaway et al., in view of Schlesinger et al., Bartenschlager, and Fields et al.

Claim 2 recites a subgenomic replicon of dengue virus origin comprising a deletion for the sequence coding for PreM and E structural proteins (.DELTA.ME). Claim 8 recites a subgenomic replicon of dengue virus type 2 origin comprising a deletion for the sequence coding for PreM and E structural proteins (.DELTA.ME).

Claim 17 recites a subgenomic replicon of dengue virus origin comprising a deletion for the sequence coding for PreM and E structural proteins (.DELTA.ME), which is adapted to receive at least a nucleotide sequence without disrupting its replication capabilities.

Claim 18 recites a vaccine comprising it, and a pharmaceutically acceptable carrier. Claim 19 recites a therapeutic comprising a subgenomic replicon of dengue virus origin which comprises a deletion for PreM and E structural proteins (.DELTA.ME), optionally which is adapted to receive at least a nucleotide sequence without disrupting its replication capabilities, and a pharmaceutically acceptable carrier.

Claim 20 recites a dengue virus like particle comprising a subgenomic replicon of dengue virus origin which comprises a deletion for the sequence coding for PreM and E structural

proteins (.DELTA.ME), optionally which is adapted to receive at least a nucleotide sequence without disrupting its replication capabilities, and structural proteins of the homologous dengue virus wherein said structural proteins encapsulate said subgenomic replicon.

Westaway et al. teaches flavivirus replicons, and further than any flavivirus RNA may be used (column 2, line 38). Westaway also teaches the 5'UTR, the nucleotide sequence coding for the nonstructural proteins, the complete or most of the 3' UTR (abstract) and deletions of the PrM and E structural proteins (Example 1).

Westaway et al. also teaches the replicons for expression of heterologous or foreign genes (column 3, line 12), thus anticipating the vaccine, the carrier, adaptation to receive a nucleotide sequence without disrupting replication capabilities. Westaway et al. also teaches a virus like particle comprising the replicon that is encapsidated (column 8, line 23).

Westaway et al. does not teach using subgenomic dengue virus replicons, specifically of dengue 2 virus.

Schlesinger et al. teaches that NS proteins from Dengue 2 virus elicit immune response. Bartenschlager et al. teaches flaviviral HCV replicons (Fig. 6). Fields et al. teaches that flaviviruses (of which dengue is a species) have structurally similar genomes. (Varnavski et al. teaching Kunjin replicons and Behrens et al. teaching pestivirus BVDV replicons are further cited in support to show the varied replicons produced from other members of Flaviviridae.)

One of ordinary skill in the art at the time the invention was made would have been motivated to construct a dengue 2 replicon comprising said deletions by combining any flaviviral replicon of Westaway et al., Dengue 2 as an immunogen in light of the other flaviviral replicons of Bartenschlager et al., and Fields et al. because Schlesinger et al.

teaches Dengue 2 NS immunogens and Bartenschlager et al., Fields et al. teach other flaviviridae replicons and Westaway et al. teaches that any flaviviral RNA may be used.

One of ordinary skill in the art at time the invention was made would have had a reasonable expectation of success for constructing a dengue 2 replicon by combining any flaviviral replicon of Westaway et al. and the other flaviviral replicons to also create a dengue 2 replicon because Schlesinger et al. teaches flavivirus Dengue 2, Bartenschlager et al., Fields et al. also teach flaviviridae genomic similarities and replicons and Westaway et al. teaches using any flaviviral RNA.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 2, 8, 16, 17-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Westaway et al., Schlesinger et al., Bartenschlager, and Fields et al. in further view of Khromykh et al.

See the recitations to claims 2, 8, 17-20 above.

Claim 16 recites a subgenomic replicon of dengue virus origin comprising a deletion for the sequence coding for PreM and E structural proteins (.DELTA.ME); and further comprising part or all of the 5'UTR; at least about the first 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94,

95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, or 175 nucleotides of C protein; at least about the last 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, or 175 nucleotides of E protein; substantially all of the nonstructural region; and part or all of the 3'UTR.

See the teachings of Westaway et al., Schlesinger et al., Bartenschlager, and Fields et al. above.

Khromykh et al. teaches subgenomic Kunjin replicons, and further, Khromykh et al. teaches a flaviviral subgenomic Kunjin replicon with PreM and E deletions. The replicons contain part or all of the 5'UTR; substantially all of the nonstructural region; part or all of the 3'UTR.

As for the C deletion, the replicon contains at least the first 319 nucleotides (position 416 minus position 97=319), which encompasses at least the first 175 nucleotides (see Fig. 1D).

As for the E deletion, the replicon retains at least the last 90 nucleotides of E protein (See Figure 1C).

One of ordinary skill in the art at the time the invention was made would have been motivated to construct the dengue 2 replicon comprising said deletions by combining the dengue 2 replicon of Westaway et al., Schlesinger et al., Bartenschlager et al., and Fields et al. and the E and C deletions of Khromykh et al. because Khromykh et al. teaches C and E deletions in flaviviral replicons and Westaway et al. teaches that any flaviviral RNA may be used.

One of ordinary skill in the art at time the invention was made would have had a reasonable expectation of success for constructing the dengue 2 replicon of Westaway et al., Schlesinger et al., Bartenschlager et al., and Fields et al. and the E and C deletions of Khromykh et al. because Westaway et al., Schlesinger et al., Bartenschlager et al., Fields et al. and Khromykh et al. teach flaviviridae genomic similarities and replicons and Westaway et al. teaches using any flaviviral RNA.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 8, 16, 17-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/194,342. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application recites a subgenomic dengue replicon comprising a deletion for the sequences coding for PreM and E structural proteins that encompass the species of a dengue replicon expressing a transgene and VLP containing the replicon recited by claims 1-12 of copending Application No. 11/194,342.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 2, 8, 16, 17-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 22-27 of copending Application No. 11/192,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application recites a subgenomic dengue replicon comprising a deletion for the sequences coding for PreM and E structural proteins that encompass the species of a dengue replicon with a deletion of PreM, specific nucleotide

sequences, a pharmaceutical composition and VLP containing the replicon recited by 1-6, 8, 22-27 of copending Application No. 11/192,923.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

M. Franco Salvoza
Patent Examiner

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600